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(57) Abstract

A human protein having a hydrophobic domain and comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10, a cDNA coding for said protein, and an expression vector comprising the cDNA as well as an eucaryotic cell comprising the cDNA. The protein can be provided by expression of the cDNA coding for such protein.

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DESCRIPTION

HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells, wherein these membrane protein genes are introduced to express secretory proteins and membrane proteins in large amounts, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Cells secrete many proteins outside the cells. These secretory proteins play important roles for the proliferation control, the differentiation induction, the material transportation, the biological protection, etc. in the cells. Different from intracellular proteins, the secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip, so that there

are hidden potentialities as medicines. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents, etc. have been currently employed as medicines. In addition, secretory proteins other than those described above have been undergoing clinical trials to develop as pharmaceuticals. Because it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes coding for them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where the genes of many of them have been cloned already. It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-cryptogenic diseases. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, these secretory proteins and membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then screening of the cells expressing

the target active protein by secretion or on the surface of membrane. However, this method is applicable only to cloning of a gene of a protein with a known function.

In general, secretory proteins and membrane proteins possess at least one hydrophobic domain inside the proteins, wherein, after synthesis thereof in the ribosome, this domain works as a secretory signal or remains in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of this cDNA for encoding the secretory proteins and the membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic domains in the amino acid sequence of the protein encoded by this cDNA.

DISCLOSURE OF INVENTION

The object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as transformation eucaryotic cells that are capable of expressing these DNAs.

As the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having hydrophobic domains, namely proteins containing any of the amino acid sequences represented by Sequence Nos. 1 to 10. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 11 to 21, 23, 25, 27, 29, 31,

33, 35, 37 and 39, as well as expression vectors that are capable of expressing any of these DNAs by in vitro translation or in eucaryotic cells and transformation eucaryotic cells that are capable of expressing these DNAs and of producing the above-mentioned proteins.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP00631.

Fig. 2 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02403.

Fig. 3 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02420.

Fig. 4 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10349.

Fig. 5 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10508.

Fig. 6 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10524.

Fig. 7 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10529.

Fig. 8 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10537.

Fig. 9 A figure depicting the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10549.

Fig. 10 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10551.

BEST MODE FOR CARRYING OUT THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the hydrophobic domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to expression of a large amount of the encoded protein by using prokaryotic cells such as *Escherichia coli, Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translation region of this cDNA is subjected to recombination to a vector having an RNA polymerase promoter, followed by addition to an in vitro translation system such as a rabbit riticulocyte

lysate or a wheat germ extract, containing an RNA polymerase corresponding to the promoter. RNA polymerase inhibitors are exemplified by T7, T3, SP6, and the like. The vectors containing these RNA polymerase inhibitors are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II, and so on. Furthermore, a membrane protein of the present invention can be expressed as the form incorporated in the microsome membrane, when a canine pancreas microsome or the like is added into the reaction system.

In the case in which a protein of the present invention is produced by expressing the DNA using a microorganism such as *Escherichia coli* etc., a recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with this expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In this case, a protein fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion coding for this cDNA can be obtained by cleavage of this fusion protein with a suitable protease. The expression vector for *Escherichia coli* is exemplified by the pUC system, pBluescript II, the pET expression system, the pGEX expression system, and so

on.

In the case in which one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be obtained by secretory production or produced as a membrane protein on the cell-membrane surface, when the translation region of this cDNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins. The expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-

exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1. to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein sugar chains are added. Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs coding for the above-mentioned proteins. These DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for

example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)$^+$ RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of an optional portion in the cDNA base sequences of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of an oligonucleotide to be hybridized at both termini of the objective cDNA fragment, followed by the usage of this oligonucleotide as the primer for the RT-PCR method from an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by containing either of the base sequences represented by Sequence Nos. 11 to 20 or the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Table 1 summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded

protein, for each of the cDNAs.

Table 1

Sequence No.	HP number	Cells	Base number	Number of amino acid residues
1, 11, 21	HP00631	Saos-2	1085	238
2, 12, 23	HP02403	Stomach cancer	1168	194
3, 13, 25	HP02420	Stomach cancer	624	139
4, 14, 27	HP10349	Stomach cancer	1121	323
5, 15, 29	HP10508	Stomach cancer	827	231
6, 16, 31	HP10524	Stomach cancer	1189	97
7, 17, 33	HP10529	Saos-2	1500	198
8, 18, 35	HP10537	Saos-2	806	140
9, 19, 37	HP10549	Stomach cancer	1718	201
10, 20, 39	HP10551	Stomach cancer	995	249

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39 shall come within the scope of the present invention.

In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 10.

The cDNAs of the present invention include cDNA fragments (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 11 to 20 or in the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

<u>Research Uses and Utilities</u>

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a

particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodiesusing DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the

corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation,

such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular

Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark,S.C.

and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial orfungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or

other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-

specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by

immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate

disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from

the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class IIα chain protein and an MHC class IIβ chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan,

A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro

assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood

84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well

as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc.,

New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of

bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be

useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or

regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

<u>Activin/Inhibin Activity</u>

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis)consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those

described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result,such a protein is expected to be useful in treatment of various coagulation disorders (includinghereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or

inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

<u>Anti-Inflammatory Activity</u>

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of ytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by

inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example,

psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is embodied in more detail by the following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

cDNA libraries (WO97/33993) of osteosarcoma cell line Saos-2 and cDNA libraries (WO97/15596) of tissues of stomach cancer delivered by the operation were used for the cDNA libraries. Full-length cDNA clones were selected from respective libraries and the whole base sequences thereof were determined to construct a homo/protein cDNA bank consisting of the full-length cDNA clones. The

hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by the full-length cDNA clones registered in the homo/protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. Any clone that has a hydrophobic region being putative as a secretory signal or a transmembrane domain in the amino acid sequence of an encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30°C for 90 minutes in a total 25 μl volume of the reaction solution containing 12.5 μl of T_NT rabbit reticulocyte lysate, 0.5 μl of a buffer solution (attached to kit), 2 μl of an amino acid mixture (methionine-free), 2 μl of [^{35}S]methionine (Amersham) (0.37 MBq/μl), 0.5 μl of T7RNA polymerase, and 20 U of RNasin. Also, an experiment in the presence of a membrane system was carried out by adding to this reaction system 2.5 μl of a canine pancreas microsome fraction (Promega). To 3 μl of the resulting reaction solution was added 2 μl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight

of the translation product was determined by carrying out the autoradiography.

(3) Expression by COS7

Escherichia coli bearing the expression vector of the protein of the present invention was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 μg/ml of ampicillin, the helper phage M13K07 (50 μ l) was added, and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 μl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The culture cells originating from the simian kidney, COS7, were incubated at 37°C in the presence of 5% CO_2 in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1×10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO_2. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 μl of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 μl of TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO_2. After the culture medium was replaced by a culture medium containing [^{35}S]cystine or

[^{35}S]methionine, the incubation was carried out for one hour. After the culture medium and the cells were separated by centrifugation, proteins in the culture fraction and the cell-membrane fraction were subjected to SDS-PAGE.

(4) Clone Examples

<HP00631> (Sequence Nos. 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP00631 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 25-bp 5'-nontranslation region, a 717-bp ORF, and a 343-bp 3'-nontranslation region. The ORF codes for a protein consisting of 238 amino acid residues and there existed five putative transmembrane domains. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS7 cells, an expression product of about 25 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the golden hamster androgen-regulated protein FAR-17 (PIR Accession No. A54313). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the golden hamster androgen-regulated protein FAR-17 (GH). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 38.0% in the entire

region.

Table 2

```
HP M-----ALVPCQVLRMAILLSYCSILCNYKAIEMPSHQTYGGSWKFLTFIDLVIQAVFFG
   *           *    * * *  *    *  *       **  * **   *  ** ***
GH MTRTTTCVYHFLVWNWYIFLNY-YIPLIGKDDEKLKEFHDGGRSKYLTLLNLLLQAIFFG
HP ICVLTDLSSLLTRGSGNQEQERQLKKLI-SLRDWMLAVLAFPVGVFVVAVFWIIYAYDRE
      * *    * *  *     *   * * * **     * **   *   ***    ***
GH VACLDD---VLKRIIG-----RKDIKFITSTRDLLFSTLVFPISTFIFLVFWTLFYYDRS
HP MIYPKLLDNFIPGWLNHGMHTTVLPFILIEMRTSHHQYPSRSSGLTAICTFSVGYILWVC
    **** **   * **** ***  * * * *     * ***   **         **  *
GH LIYPKGLDDYFPAWLNHAMHTYILLFVLVETILRPHHYPSKKLGLALLGACNLAYITRVL
HP WVHHVTGMWVYPFLEHIGPGARIIFFGSTTIIMNFLYLLGEVLNNYIW-DTQKSMEEEKE
   *    ** ****      *   ****    **    ** **  *   *  * *
GH WRYSQTGNWVYPVFASLNPLGIIIFFLVCYILNASIYLVGEKINHWKWGATVK---PLMK
HP KPKLE
   * *
GH KKK--
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R22829) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02403> (Sequence Nos. 2, 12, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP02403 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 6-bp 5'-nontranslation region, a 585-bp ORF, and a 577-

bp 3'-nontranslation region. The ORF codes for a protein consisting of 194 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 21,959 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the Japanese quail apoptosis regulator NR-13 (SWISS-PROT Accession No. Q90343). Table 3 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the Japanese quail apoptosis regulator NR-13 (CC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 31.5% in the entire region.

Table 3

```
HP MADPLRERTELLLADYLGYCAREPGTPEPAPSTPEAAVLRSAAARLRQIHRSFF--SAYL
   *   * * * *** **    *   *     **   ** ** *** *    * **   * *
CC MPGSLKEETALLLEDYFQHRA---GGAALPPS-ATAAELRRAAAELERRERPFFRSCAPL
HP GYPGNRFELVAL--MADSVLSDSPGPTWGRVVTLVTFAGTLLERGPLVTARWKKWGFQPR
        * *  **       *    *  ***   ** *****
CC ARAEPR-EAAALLRKVAAQLETDGGLNWGRLLALVVFAGTL------------------A
HP LKEQEGDVARDCQRLVALLSSRLMGQHRAWLQAQGGWDGFCHFF-RTPFPLAFWRKQLVQ
       *        ** * *   *      *    ******* ** *     *     *
CC AALAESACEEGPSRLAAALTAYLAEEQGEWMEEHGGWDGFCRFFGRHGSQPADQNSTLSN
HP A-FLSCLLTTAFIYLWTRLL
   *         *
CC AIMAAAGFGIAGLAFLLVVR
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA098865) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02420> (Sequence Nos. 3, 13, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP02420 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 35-bp 5'-nontranslation region, a 420-bp ORF, and a 169-bp 3'-nontranslation region. The ORF codes for a protein consisting of 139 amino acid residues and there existed three putative transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 17 kDa that was almost identical with the molecular weight of 16,082 predicted from the ORF. When expressed in CO7 cells, an expression product of about 16 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to a yeast hypothetical protein of 15.9 kDa (SWISS-PROT Accession No. P53173). Table 4 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the yeast hypothetical protein of 15.9 kDa (SC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 43.2% in the entire region.

Table 4

```
HP MEAVVFVFSLLDCCALIFLSVYFIITLSDLECDYINARSCCSKLNKWVIPELIGHTIVTV
   *.* .*..... * .*    *.*.*  .*** ****. . ***.** ..**   *. ...
SC MGAWLFILAVVVNCINLFGQVHFTILYADLEADYINPIELCSKVNKLITPEAALHGALSL
HP  LLIMSLHWFIFLLNLPVATWNIYRYIMVPSGNMGVFDPTEIHNRGQLKSHMKEAMIKLGF
    *.*.. .**.******* .   *.  ..  ... ..*.***  *. * .*..*...****
SC  LFLLNGYWFVFLLNLPVLA---YNLNKI-YNKVQLLDATEIF-RT-LGKHKRESFLKLGF
HP  HLLCFFMYLYSMILALIND
    *** **.***.**.***..
SC  HLLMFFFYLYRMIMALIAESGDDF
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA044799) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10349> (Sequence Nos. 4, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10349 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 16-bp 5'-nontranslation region, a 972-bp ORF, and a 133-bp 3'-nontranslation region. The ORF codes for a protein consisting of 323 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 36,200 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. F13066) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10508> (Sequence Nos. 5, 15, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10508 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of

a 33-bp 5'-nontranslation region, a 696-bp ORF, and a 98-bp 3'-nontranslation region. The ORF codes for a protein consisting of 231 amino acid residues and there existed four transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in CO7 cells, an expression product of about 22 kDa was observed in the supernatant fraction and the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA484181) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10524> (Sequence Nos. 6, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP10524 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 308-bp 5'-nontranslation region, a 294-bp ORF, and a 587-bp 3'-nontranslation region. The ORF codes for a protein consisting of 97 amino acid residues and possessed one transmembrane domain. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 21 kDa that was larger than the molecular weight of 10,673 predicted from the ORF. When expressed in COS cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the human glycophorin C (SWISS-PROT Accession No. P04921). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the human glycophorin C (GP). Therein, the marks of - and * represent a gap and an amino acid residue identical with the protein of the present invention, respectively. The both proteins possessed a homology of 30.5% in the entire region.

Table 5

```
HP M------------TSLLTTP---SPREELMTTPILQPTEALS-PEDG---AST------A
   *             **   *   *      ** *  *    *   **    **
GP MWSTRSPNSTAWPLSLEPDPGMASASTTMHTTTIAEPDPGMSGWPDGRMETSTPTIMDIV
HP LIAVVITVVFLTLLSVVILIFFYLYKNKGSYVTYE--PTEGEPSAIVQMESD----LAKG
    ** **  *   * *       * *  ** * * *   **   **      *     *
GP VIAGVIAAVAIVLVSLLFVMLRYMYRHKGTYHTNEAKGTEFAESADAALQGDPALQDAGD
HP SEKEEYFI
   *   ****
GP SSRKEYFI
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R21992) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10529> (Sequence Nos. 7, 17, and 33)

Determination of the whole base sequence of the cDNA insert of clone HP10529 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 93-bp 5'-nontranslation region, a 597-bp ORF, and an 810-bp 3'-nontranslation region. The ORF codes for a protein consisting of 198 amino acid residues and possessed two transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the fugu rubripes putative protein 2 (GenBank Accession No. AF026198). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the fugu rubripes putative protein 2 (FR). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 56.1% in the entire region.

Table 6

```
HP MATLWGGLLRLGSLLSLSCLAL-SVLLLAQLS-DAAKNFEDVRCKCICPPYKENSGHIYN
                     .*  *. .** ...**.... ..**.*.************.. ******
FR       MPSDREGLWMLAAFALMTLFLLDNVGVTQAKSFDDVRCKCICPPYRNISGHIYN
HP KNISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSIILGLLLLY
   .*..****.*****.****.* ******* *********. **.*****.**..* ****
FR RNFTQKDCNCLHVVDPMPVPGNDVEAYCLLCECKYEERSTNTIRVTIIIFLSVVGALLLY
HP MVYLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQR
   *..* **.*.....    ** .....* .* **      .. .  .  .  ..**..** ****
FR MLFLLLVDPLIRKPD-PLAQTLHNEEDSEDIQP------QMSGDPARGNTVLERVEGAQQR
HP WKLQVQEQRKSVFDRHVVLS
   ** *******.***** .*
FR WKKQVQEQRKTVFDRHKML
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N33899) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10537> (Sequence Nos. 8, 18, and 35)

Determination of the whole base sequence of the cDNA insert of clone HP10537 obtained from cDNA libraries of the human osteosarcoma cell line Saos-2 revealed the structure consisting of a 94-bp 5'-nontranslation region, a 423-bp ORF, and a 289-bp 3'-nontranslation region. The ORF codes for a protein consisting of 140 amino acid residues and possessed four putative transmembrane domains. Figure 8 depicts the hydrophobicity/hydrophilicity profile,

obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS cells, an expression product of about 14 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R36207) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10549> (Sequence Nos. 9, 19, and 37)

Determination of the whole base sequence of the cDNA insert of clone HP10549 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of an 11-bp 5'-nontranslation region, a 606-bp ORF, and a 1101-bp 3'-nontranslation region. The ORF codes for a protein consisting of 201 amino acid residues and possessed three putative transmembrane domains. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was larger than the molecular weight of 23,346 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N28687) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10551> (Sequence Nos. 10, 20, and 39)

Determination of the whole base sequence of the cDNA insert of clone HP10551 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of a 152-bp 5'-nontranslation region, a 750-bp ORF, and a 93-bp 3'-nontranslation region. The ORF codes for a protein consisting of 249 amino acid residues and possessed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the nematode imaginary protein T15B7 (GenBank Accession No. F022985). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode imaginary protein T15B7 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 41.3% in the entire region.

Table 7

```
HP MASSDEDGTNGGASEAGEDREAPGKRRRLGFLATAWLTFYDIAMTAGWLVLAIAMVRFYM
                                     ..*. *..  . ** .. .  *
SC                               MSVQTYLVAYNVLQILGWSAILVKTVLGLA
HP EKGTHRGLYKSIQKTLKFFQTFALLEIVHCLIGIVPTSVIVTGVQVSSRIFMVWLITHSI
   .  * . **.*.. .**.*** *.**..* ..*.*...* .*..**.**. .** * *
SC NGLTWPQLYESVEFELKIFQTAAILEVIHAIVGLVRSPVGTTAMQVTSRVVLVWPILHLC
HP KPIQNEESVVLFLVAWTVTEITRYSFYTFSLLDH-LPYFIKWARYNFFIILYPVGVAGEL
   .. . . .* *.****.***..*****..*.*.. .***. . **..* .***.**.***
SC STARFSIGVPLLLVAWSVTEVIRYSFYALSVLKQPIPYFLLYLRYTLFYVLYPMGVSGEL
HP LTIYAALPHVKKTGMFSIRLPNKYNVSFDYYYFLLITMASYIPLFPQLYFHMLRQRRKVL
   **..*.* .*... .... .**. *....... *.*.  **** ******.*. **.*.*
SC LTLFASLNEVDEKKILTLEMPNRLNMGISFWWVLIIAALSYIPGFPQLYFYMIGQRKKIL
HP HGEVIVEKDD
    *
SC GGGSKKKQLIATNQNSTLFINYSPKTKRQWKCFSAEFVDILCSPFGIFVIVIREESWKSN
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N67509) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. All of the proteins of the present invention are secreted or exist in the cell

membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells, wherein these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is

a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal

et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein,

where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.
Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions,

more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA : DNA	≥50	65℃; 1×SSC -or- 42℃; 1×SSC,50% formamide	65℃; 0.3×SSC
B	DNA : DNA	<50	T_B*; 1×SSC	T_B*; 1×SSC
C	DNA : RNA	≥50	67℃; 1×SSC -or- 45℃; 1×SSC,50% formamide	67℃; 0.3×SSC
D	DNA : RNA	<50	T_D*; 1×SSC	T_D*; 1×SSC
E	RNA : RNA	≥50	70℃; 1×SSC -or- 50℃; 1×SSC,50% formamide	70℃; 0.3×SSC
F	RNA : RNA	<50	T_F*; 1×SSC	T_F*; 1×SSC
G	DNA : DNA	≥50	65℃; 4×SSC -or- 42℃; 4×SSC,50% formamide	65℃; 1×SSC
H	DNA : DNA	<50	T_H*; 4×SSC	T_H*; 4×SSC
I	DNA : RNA	≥50	67℃; 4×SSC -or- 45℃; 4×SSC,50% formamide	67℃; 1×SSC
J	DNA : RNA	<50	T_J*; 4×SSC	T_J*; 4×SSC
K	RNA : RNA	≥50	70℃; 4×SSC -or- 50℃; 4×SSC,50% formamide	67℃; 1×SSC
L	RNA : RNA	<50	T_L*; 2×SSC	T_L*; 2×SSC
M	DNA : DNA	≥50	50℃; 4×SSC -or- 40℃; 6×SSC,50% formamide	50℃; 2×SSC
N	DNA : DNA	<50	T_N*; 6×SSC	T_N*; 6×SSC
O	DNA : RNA	≥50	55℃; 4×SSC -or- 42℃; 6×SSC,50% formamide	55℃; 2×SSC
P	DNA : RNA	<50	T_P*; 6×SSC	T_P*; 6×SSC
Q	RNA : RNA	≥50	60℃; 4×SSC -or- 45℃; 6×SSC,50% formamide	60℃; 2×SSC
R	RNA : RNA	<50	T_R*; 4×SSC	T_R*; 4×SSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.
†: SSPE (1×SSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.
*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10℃ less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(℃)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(℃)=81.5 + 16.6($\log_{10}[Na^+]$) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the

hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10.

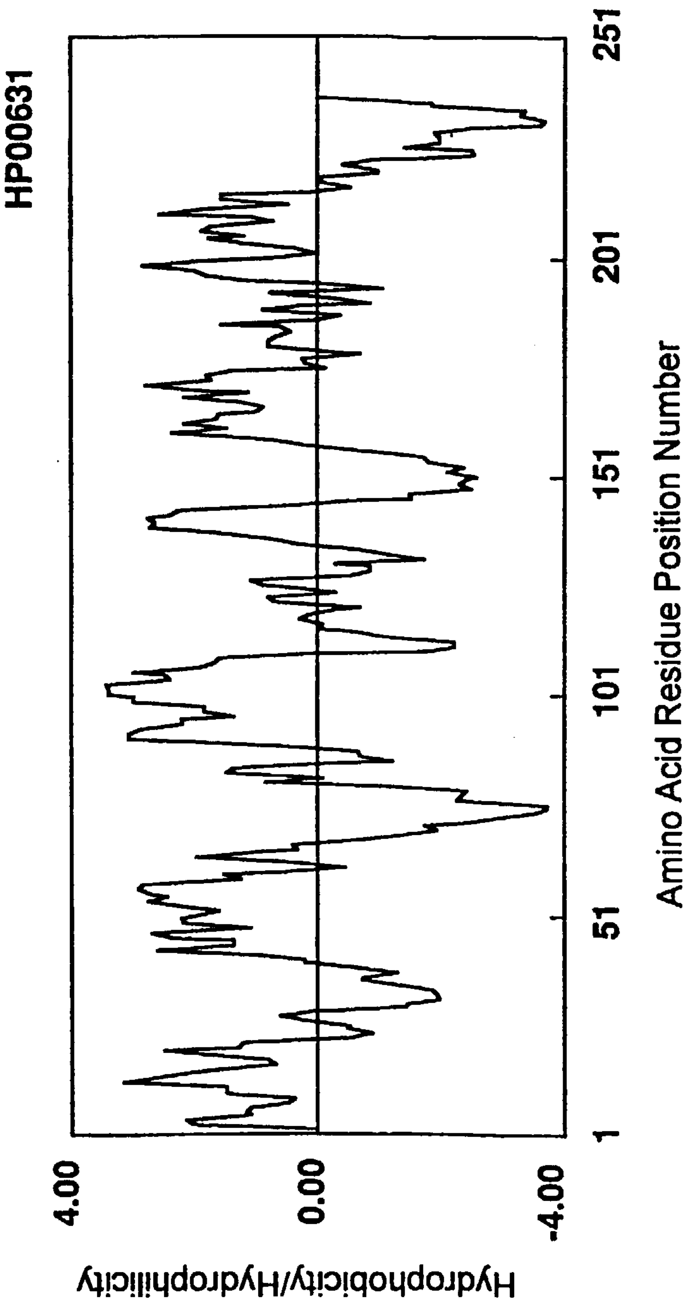
2. A DNA coding for the protein according to Claim 1.

3. A cDNA comprising any of the base sequences represented by Sequence Nos. 11 to 20.

4. The cDNA according to Claim 3 comprising any of the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

5. An expression vector capable of expressing the DNA according to any of Claims 2 to 4 by in vitro translation or in eucaryotic cells.

6. A transformation eucaryotic cell capable of expressing the DNA according to any of Claims 2 to 4 to produce the protein according to Claim 1.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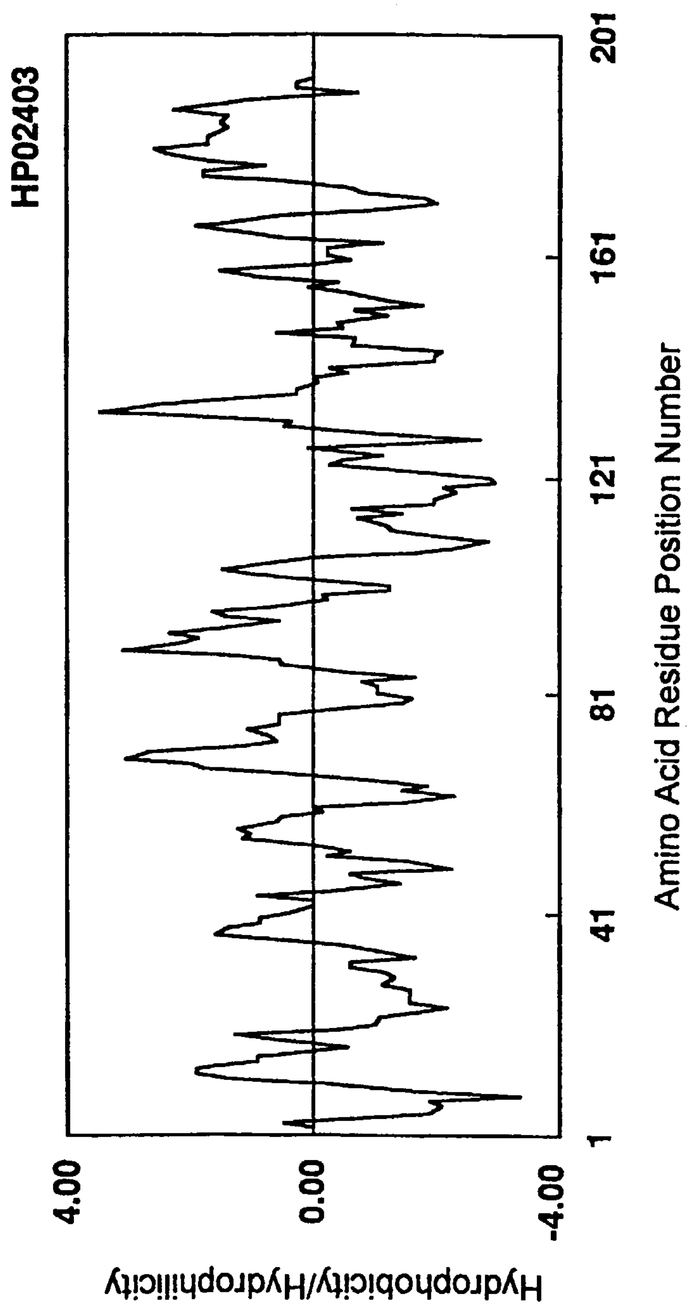
101
151
201
251
Amino Acid Residue Position Number

Fig. 1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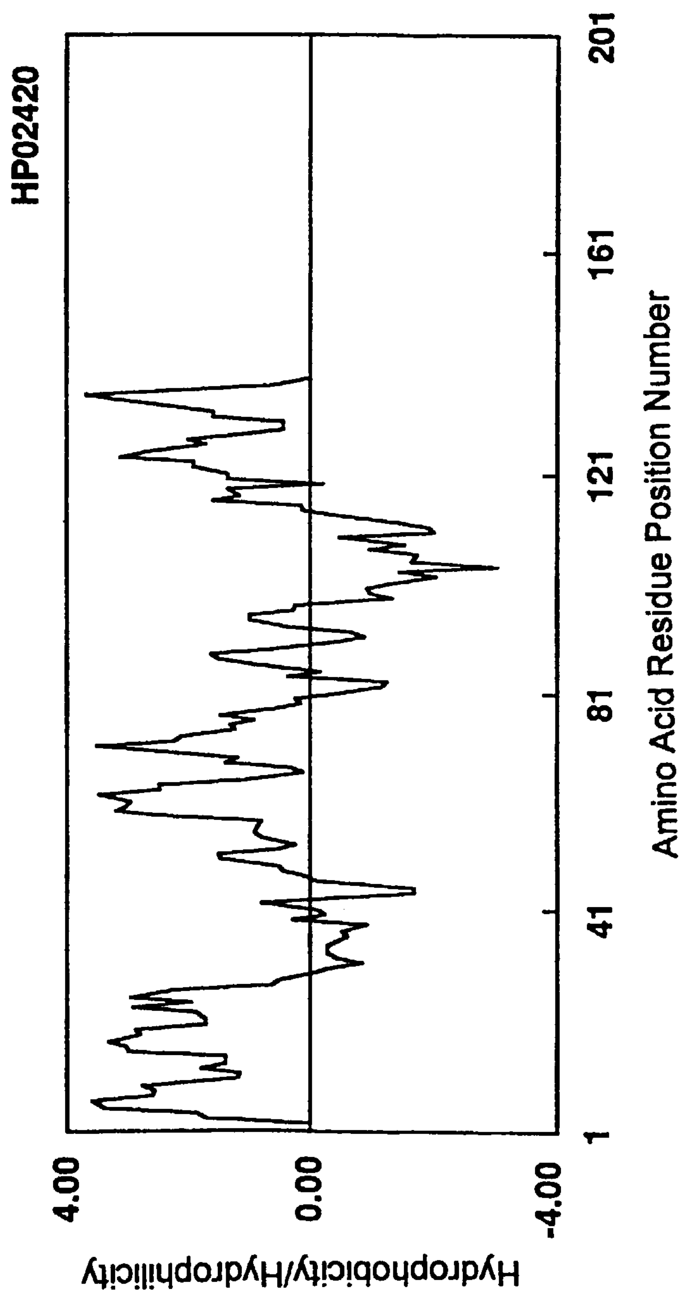
Amino Acid Residue Position Number

Fig. 2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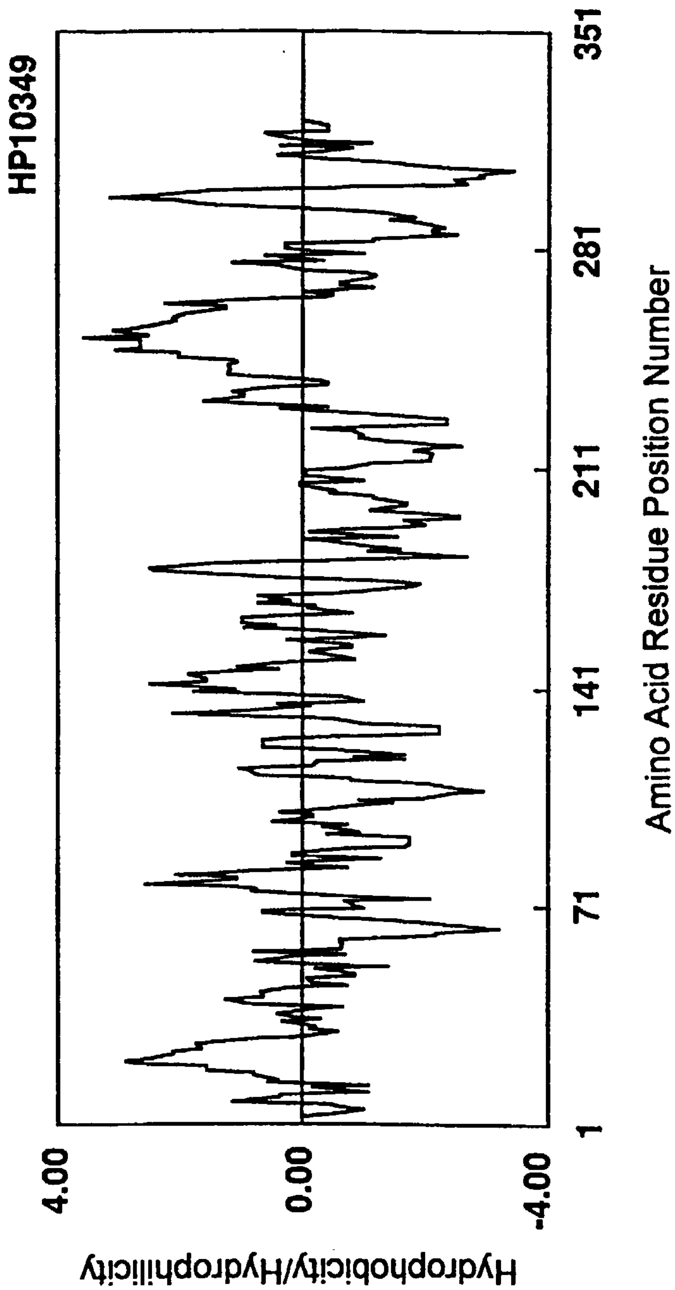
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Amino Acid Residue Position Number

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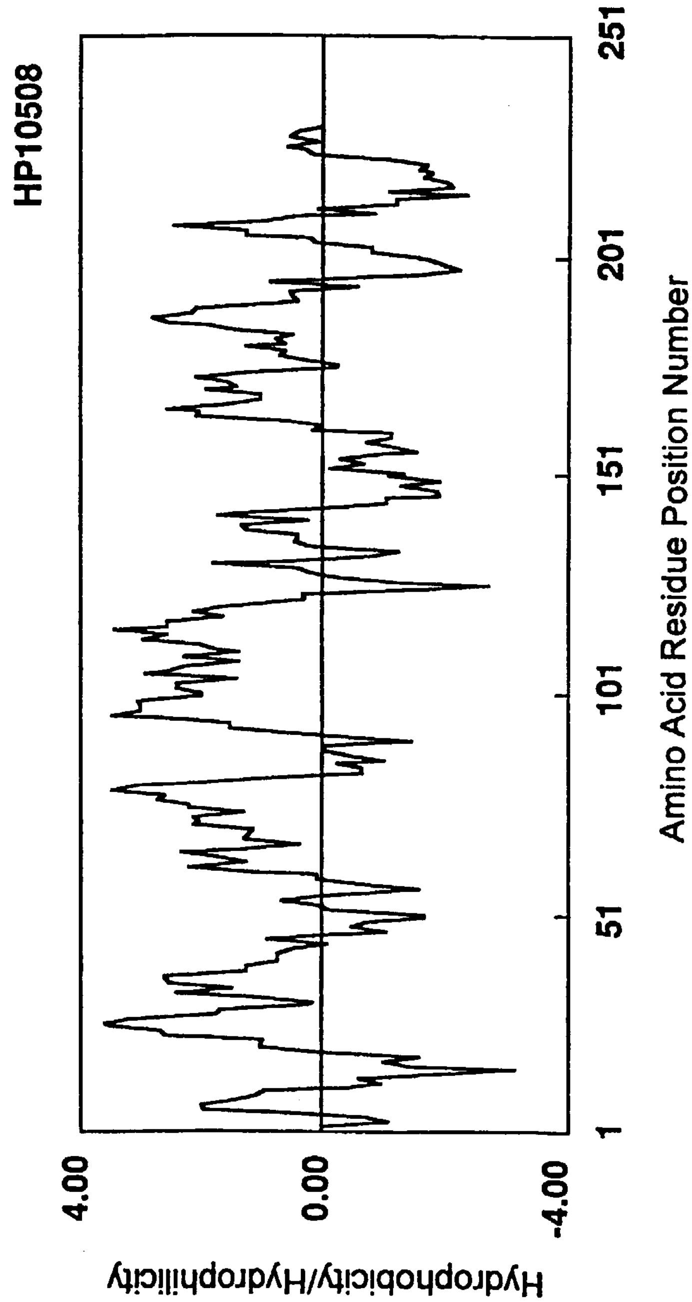
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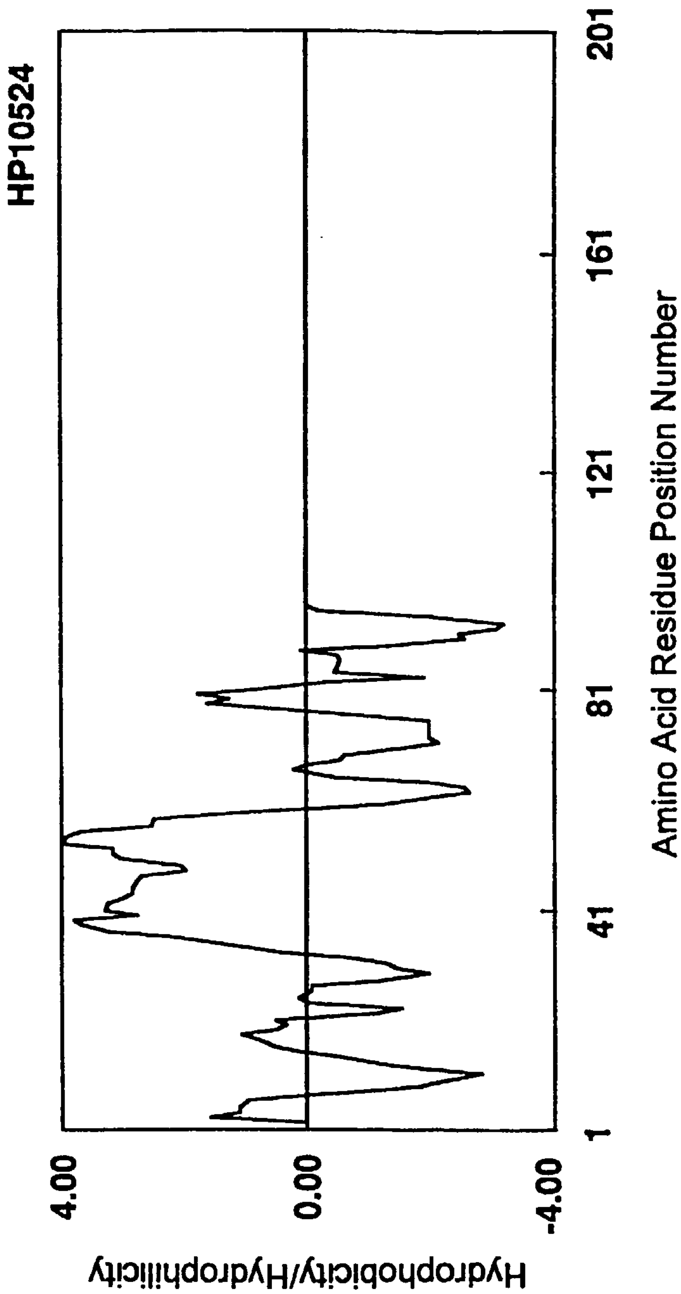
Amino Acid Residue Position Number

Fig. 5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161
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Amino Acid Residue Position Number

Fig. 6

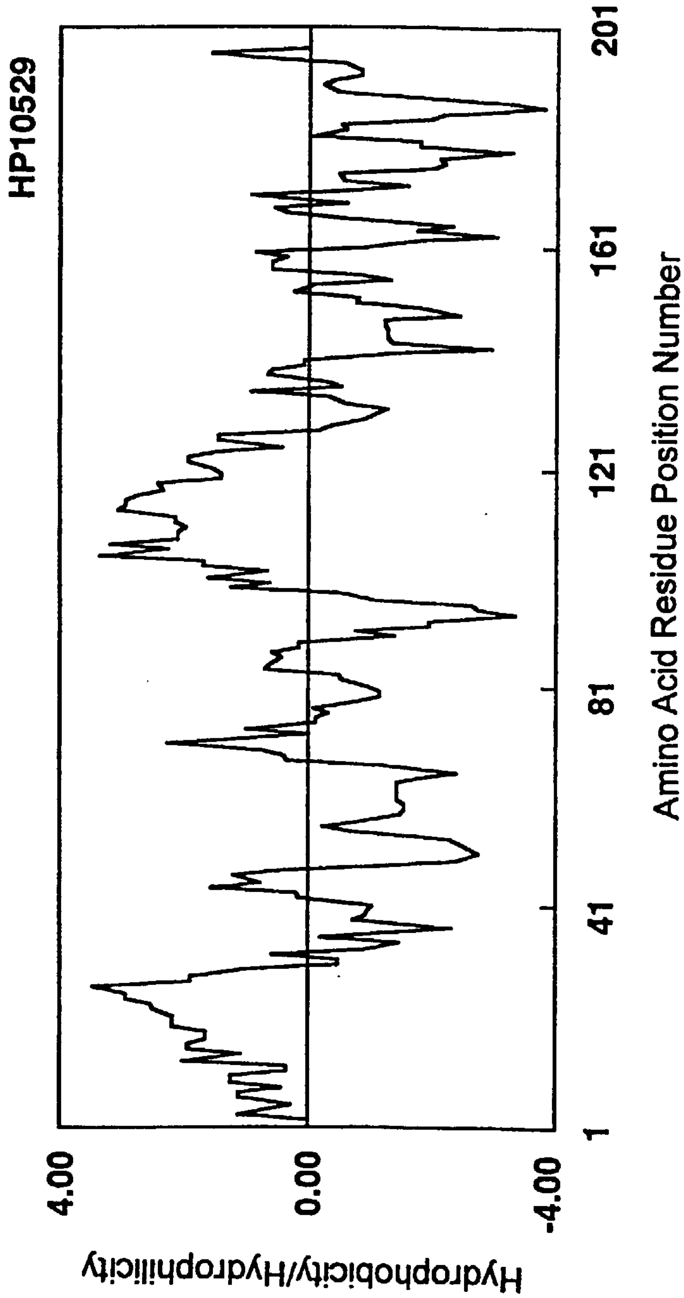
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Fig. 7

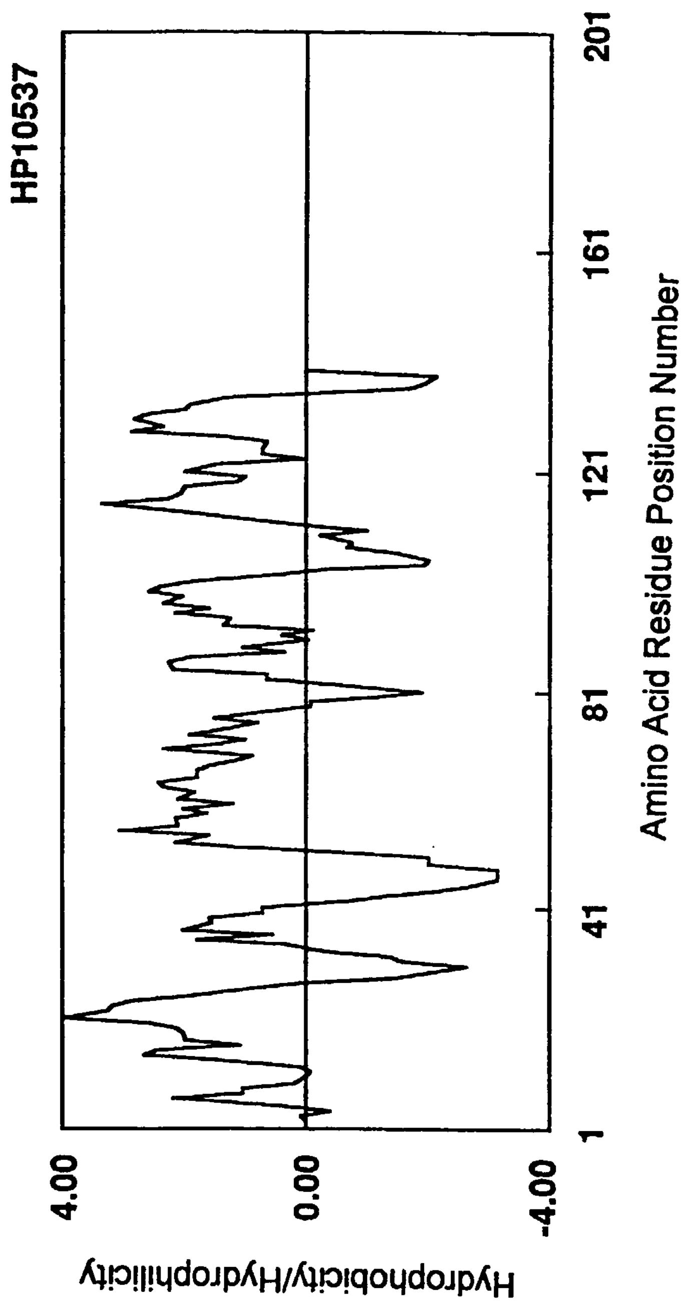
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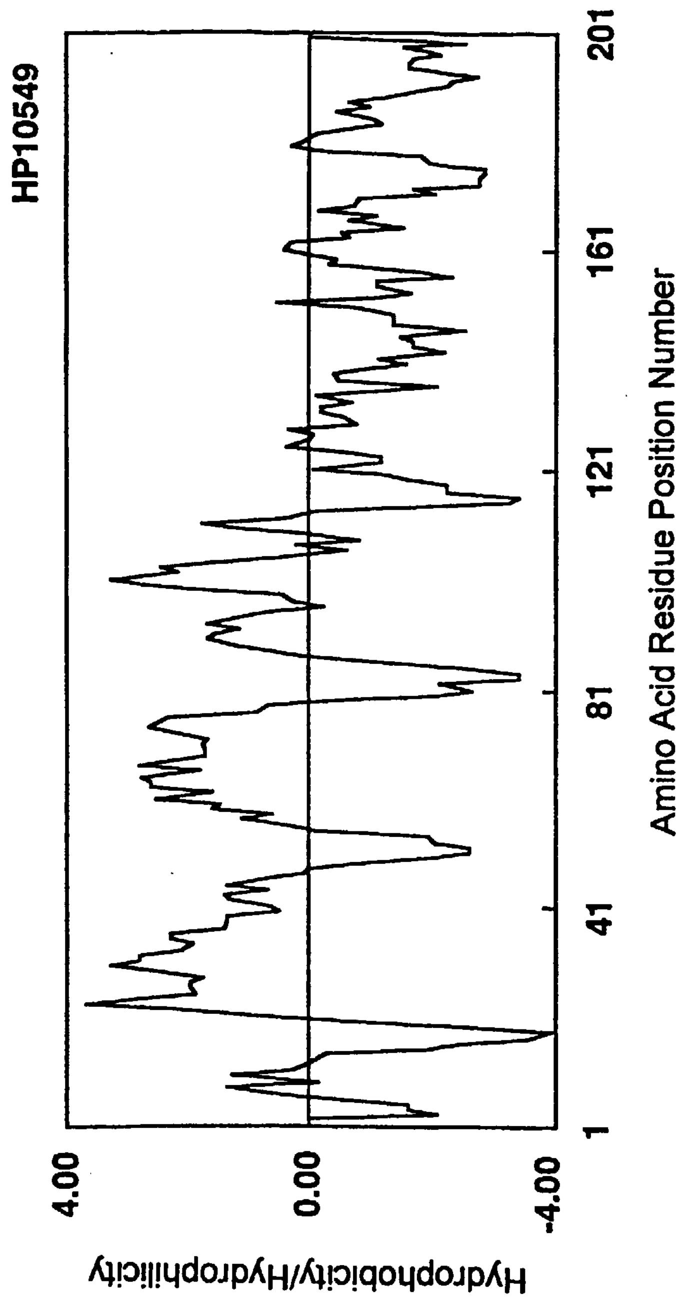
Fig. 8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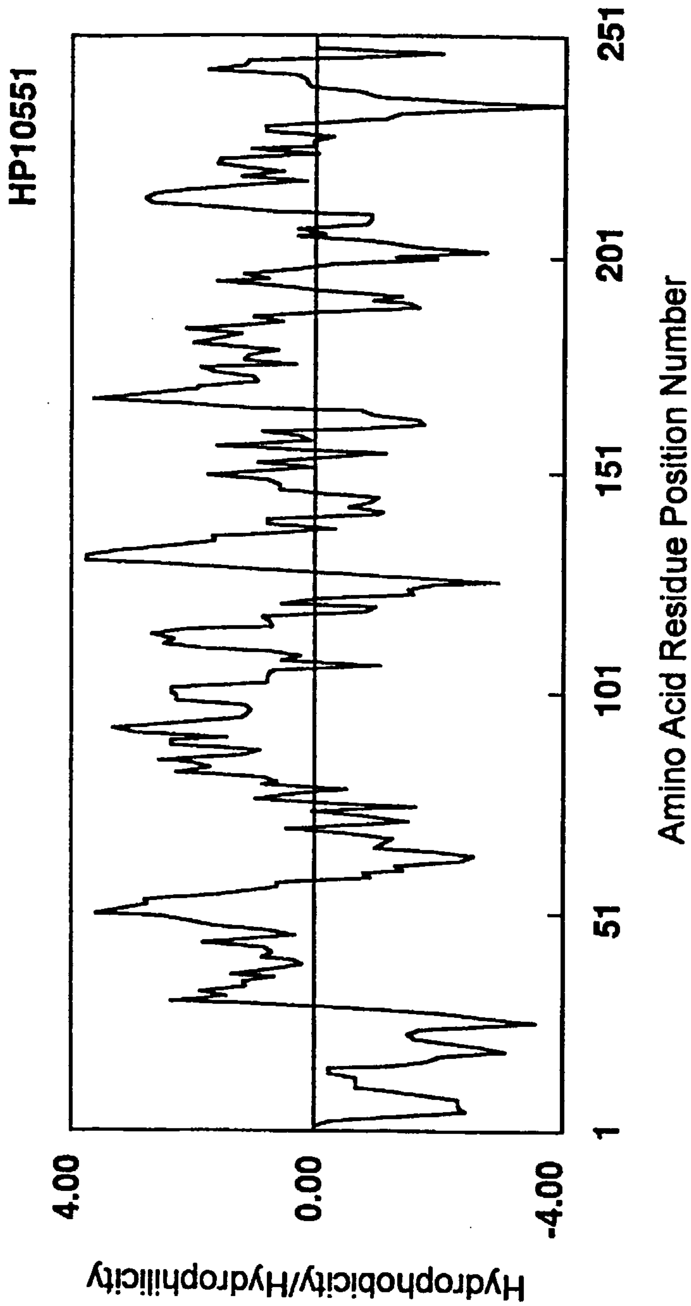
Hydrophobicity/Hydrophilicity

Fig. 9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Amino Acid Residue Position Number

Fig. 10

Sequence listing

<110> Sagami Chemical Research Center et al.

<120> Human Proteins Having Hydrophobic Domains And DNAs Encoding These Proteins

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<141> 1999-06-18

<150> JP 10-180008
<151> 1998-06-26

<160> 40

<170> Windows 95 (Word 98)

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Gln Thr Tyr Gly Gly Ser Trp Lys Phe Leu Thr Phe Ile Asp Leu Val
         35                  40                  45
Ile Gln Ala Val Phe Phe Gly Ile Cys Val Leu Thr Asp Leu Ser Ser
     50                  55                  60
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Lys Leu Ile Ser Leu Arg Asp Trp Met Leu Ala Val Leu Ala Phe Pro
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Val Gly Val Phe Val Val Ala Val Phe Trp Ile Ile Tyr Ala Tyr Asp
100 105 110
Arg Glu Met Ile Tyr Pro Lys Leu Leu Asp Asn Phe Ile Pro Gly Trp
115 120 125
Leu Asn His Gly Met His Thr Thr Val Leu Pro Phe Ile Leu Ile Glu
130 135 140
Met Arg Thr Ser His His Gln Tyr Pro Ser Arg Ser Ser Gly Leu Thr
145 150 155 160
Ala Ile Cys Thr Phe Ser Val Gly Tyr Ile Leu Trp Val Cys Trp Val
165 170 175
His His Val Thr Gly Met Trp Val Tyr Pro Phe Leu Glu His Ile Gly
180 185 190
Pro Gly Ala Arg Ile Ile Phe Phe Gly Ser Thr Thr Ile Leu Met Asn
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Phe Leu Tyr Leu Leu Gly Glu Val Leu Asn Asn Tyr Ile Trp Asp Thr
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        50                  55                  60
Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp Ser Pro
65                  70                  75                  80
Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala Gly Thr
                85                  90                  95
Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys Trp Gly
            100                 105                 110
Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg Asp Cys
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    130                 135                 140
Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His Phe Phe
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35 40 45

Ile Pro Glu Leu Ile Gly His Thr Ile Val Thr Val Leu Leu Leu Met

50 55 60

Ser Leu His Trp Phe Ile Phe Leu Leu Asn Leu Pro Val Ala Thr Trp

65 70 75 80

Asn Ile Tyr Arg Tyr Ile Met Val Pro Ser Gly Asn Met Gly Val Phe

85 90 95

Asp Pro Thr Glu Ile His Asn Arg Gly Gln Leu Lys Ser His Met Lys

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Leu Tyr Ser Met Ile Leu Ala Leu Ile Asn Asp

130 135

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<212> PRT

<213> Homo sapiens

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35 40 45

His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr Tyr Pro Lys Glu

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Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu Phe Ser Ile Cys

65 70 75 80

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            100                 105                 110
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        115                 120                 125
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    130                 135                 140
Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp Ser Ala Gln Ser
145                 150                 155                 160
Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala Asp Asp Gly Lys
                165                 170                 175
Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr Ala Pro His Leu
            180                 185                 190
Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu Ser Lys Met Ser
        195                 200                 205
Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn Phe Leu Glu Asp
    210                 215                 220
Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu Asn Ser Gly Trp
225                 230                 235                 240
Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val Leu Leu Trp Ile
                245                 250                 255
Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr Val Pro Ser Glu
            260                 265                 270
Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn Glu Gln Lys Leu
        275                 280                 285
Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg Ser Lys Thr Glu
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<213> Homo sapiens

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35 40 45
Asn Pro Arg Gly Ala Val Thr Pro Glu Tyr Thr Val Ala Asn Val Ile
50 55 60
Ser Val Gly Ser Gly Leu Leu Ser Val Ser Val Gly Leu Val Ala Leu
65 70 75 80
Leu Ala Ser Arg Asn Leu Leu Arg Pro Pro Leu His Trp Val Leu Leu
85 90 95
Ala Leu Ala Leu Val Asn Leu Leu Leu Ser Val Ala Cys Ser Leu Gly
100 105 110
Leu Leu Leu Ala Val Ser Leu Thr Val Ala Asn Gly Gly Arg Arg Leu
115 120 125
Ile Ala Asp Cys His Pro Gly Leu Leu Asp Pro Leu Val Pro Leu Asp
130 135 140
Glu Gly Pro Gly His Thr Asp Cys Pro Phe Asp Pro Thr Arg Ile Tyr
145 150 155 160
Asp Thr Ala Leu Ala Leu Trp Ile Pro Ser Leu Leu Met Ser Ala Gly
165 170 175
Glu Ala Ala Leu Ser Gly Tyr Cys Cys Val Ala Ala Leu Thr Leu Arg
180 185 190
Gly Val Gly Pro Cys Arg Lys Asp Gly Leu Gln Gly Gln Val Val Ala
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Gly Ile Lys Val Lys Ala Leu

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<213> Homo sapiens

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Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn Lys Gly

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<211> 198

<212> PRT

<213> Homo sapiens

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Ala Ala Lys Asn Phe Glu Asp Val Arg Cys Lys Cys Ile Cys Pro Pro

35 40 45

Tyr Lys Glu Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys

50 55 60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro

65 70 75 80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg

85 90 95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu

100 105 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile

115 120 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp

130 135 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala

145 150 155 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Ala Gln

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Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Ser Val Phe Asp

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Arg His Val Val Leu Ser

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<212> PRT

<213> Homo sapiens

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35 40 45
Gln Asp Ile Gln Leu Val Ala Ala Leu Ser Val Thr Leu Gly Leu Phe
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Ala Val Glu Leu Ala Gly Phe Leu Ser Gly Val Ser Met Phe Asn Ser
65 70 75 80
Thr Gln Ser Leu Ile Ser Ile Gly Ala His Cys Ser Ala Ser Val Ala
85 90 95
Leu Ser Phe Phe Ile Phe Glu Arg Trp Glu Cys Thr Thr Tyr Trp Tyr
100 105 110
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Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly Ser Phe Thr
35 40 45
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50 55 60

Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu Pro Asp Phe

65 70 75 80

Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu Ala Ala Asn

85 90 95

Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe Trp Leu Leu

100 105 110

Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp Ala Phe Cys

115 120 125

Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn Arg Ala Tyr

130 135 140

Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly Asp Thr Leu

145 150 155 160

Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln Pro Pro Gln

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Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser Pro Tyr Lys

180 185 190

Asp Tyr Glu Val Lys Lys Glu Gly Ser

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<213> Homo sapiens

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35 40 45

Leu Val Leu Ala Ile Ala Met Val Arg Phe Tyr Met Glu Lys Gly Thr
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65 70 75 80
Thr Phe Ala Leu Leu Glu Ile Val His Cys Leu Ile Gly Ile Val Pro
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100 105 110
Val Trp Leu Ile Thr His Ser Ile Lys Pro Ile Gln Asn Glu Glu Ser
115 120 125
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130 135 140
Ser Phe Tyr Thr Phe Ser Leu Leu Asp His Leu Pro Tyr Phe Ile Lys
145 150 155 160
Trp Ala Arg Tyr Asn Phe Phe Ile Ile Leu Tyr Pro Val Gly Val Ala
165 170 175
Gly Glu Leu Leu Thr Ile Tyr Ala Ala Leu Pro His Val Lys Lys Thr
180 185 190
Gly Met Phe Ser Ile Arg Leu Pro Asn Lys Tyr Asn Val Ser Phe Asp
195 200 205
Tyr Tyr Tyr Phe Leu Leu Ile Thr Met Ala Ser Tyr Ile Pro Leu Phe
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<212> DNA

<213> Homo sapiens

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atacacaatc gagggcagct gaagtcacac atgaaagaag ccatgatcaa gcttggtttc 360
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gatacagcct tggctctctg gatcccttct ttgctcatgt ctgcagggga ggctgctcta 540
tctggttact gctgtgtggc tgcactcact ctacgtggag ttgggccctg caggaaggac 600
ggacttcagg ggcaggtagt agctgggtgt gacgcaagag tgaaacagaa agcctggcag 660
ccacggtttc ctgggattaa agtcaaagca tta 693

<210> 16
<211> 291
<212> DNA
<213> Homo sapiens

<400> 16
atgaccagcc tcctgactac tccttctcca agagaagaac tgatgaccac cccaatttta 60
cagcccactg aggccctgtc cccagaagat ggagccagca cagcactcat tgcagttgtt 120

atcaccgttg tcttcctcac cctgctctcg gtcgtgatct tgatcttctt ttacctgtac 180
aagaacaaag gcagctacgt cacctatgaa cctacagaag gtgagcccag tgccatcgtc 240
cagatggaga gtgacttggc caagggcagc gagaaagagg aatatttcat c 291

<210> 17
<211> 594
<212> DNA
<213> Homo sapiens

<400> 17
atggcgaccc tgtggggagg ccttcttcgg cttggctcct tgctcagcct gtcgtgcctg 60
gcgctttccg tgctgctgct ggcgcagctg tcagacgccg ccaagaattt cgaggatgtc 120
agatgtaaat gtatctgccc tccctataaa gaaaattctg ggcatattta taataagaac 180
atatctcaga aagattgtga ttgccttcat gttgtggagc ccatgcctgt gcggggggcct 240
gatgtagaag catactgtct acgctgtgaa tgcaaatatg aagaaagaag ctctgtcaca 300
atcaaggtta ccattataat ttatctctcc attttgggcc ttctacttct gtacatggta 360
tatcttactc tggttgagcc catactgaag aggcgcctct ttggacatgc acagttgata 420
cagagtgatg atgatattgg ggatcaccag ccttttgcaa atgcacacga tgtgctagcc 480
cgctcccgca gtcgagccaa cgtgctgaac aaggtagaat atgcacagca gcgctggaag 540
cttcaagtcc aagagcagcg aaagtctgtc tttgaccggc atgttgtcct cagc 594

<210> 18
<211> 420
<212> DNA
<213> Homo sapiens

<400> 18
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gtcgtcatca ccttattctg gtcccgggac agcaacatac aggcctgcct gcctctcacg 120
ttcacccccg aggagtatga caagcaggac attcagctgg tggccgcgct ctctgtcacc 180
ctgggcctct ttgcagtgga gctggccggt ttcctctcag gagtctccat gttcaacagc 240
acccagagcc tcatctccat tggggctcac tgtagtgcat ccgtggccct gtccttcttc 300

atattcgagc gttgggagtg cactacgtat tggtacattt ttgtcttctg cagtgccctt 360
ccagctgtca ctgaaatggc tttattcgtc accgtctttg ggctgaaaaa gaaacccttc 420

<210> 19
<211> 603
<212> DNA
<213> Homo sapiens

<400> 19
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tttgtcctcc tgctcaccta cgtcctcttc ttgatggcgc tgaccttcct catgtcctcc 120
ttcaccttct gtggttcctt cacgggctgg aagagacatg ggcccacat ctacctcacg 180
atgctcctct ccattgccat ctgggtggcc tggatcaccc tgctcatgct tcctgacttt 240
gaccgcaggt gggatgacac catcctcagc tccgccttgg ctgccaatgg ctgggtgttc 300
ctgttggctt atgttagtcc cgagttttgg ctgctcacaa agcaacgaaa ccccatggat 360
tatcctgttg aggatgcttt ctgtaaacct caactcgtga agaagagcta tggtgtggag 420
aacagagcct actctcaaga ggaaatcact caaggttttg aagagacagg ggacacgctc 480
tatgccccct attccacaca ttttcagctg cagaaccagc ctccccaaaa ggaattctcc 540
atcccacggg cccacgcttg gccgagccct tacaaagact atgaagtaaa gaaagagggc 600
agc 603

<210> 20
<211> 747
<212> DNA
<213> Homo sapiens

<400> 20
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gaggctcccg gcaagcggag gcgcctgggg ttcttggcca ccgcctggct caccttctac 120
gacatcgcca tgaccgcggg gtggttggtt ctagctattg ccatggtacg tttttatatg 180
gaaaaaggaa cacacagagg tttatataaa agtattcaga agacacttaa atttttccag 240
acatttgcct tgcttgagat agttcactgt ttaattggaa ttgtacctac ttctgtgatt 300

gtgactgggg tccaagtgag ttcaagaatc tttatggtgt ggctcattac tcacagtata 360
aaaccaatcc agaatgaaga gagtgtggtg ctttttctgg tcgcgtggac tgtgacagag 420
atcactcgct attccttcta cacattcagc cttcttgacc acttgccata cttcattaaa 480
tgggccagat ataatttttt tatcatctta tatcctgttg gagttgctgg tgaacttctt 540
acaatatacg ctgccttgcc gcatgtgaag aaaacaggaa tgttttcaat aagacttcct 600
aacaaataca atgtctcttt tgactactat tattttcttc ttataaccat ggcatcatat 660
atacctttgt ttccacaact ctattttcat atgttacgtc aaagaagaaa ggtgcttcat 720
ggagaggtga ttgtagaaaa ggatgat 747

<210> 21
<211> 1085
<212> DNA
<213> Homo sapiens

<400> 21
cagccggtcc aggcctctgg cgaac atg gcg ctt gtc ccc tgc cag gtg ctg 52
Met Ala Leu Val Pro Cys Gln Val Leu
1 5
cgg atg gca atc ctg ctg tct tac tgc tct atc ctg tgt aac tac aag 100
Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser Ile Leu Cys Asn Tyr Lys
10 15 20 25
gcc atc gaa atg ccc tca cac cag acc tac gga ggg agc tgg aaa ttc 148
Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe
30 35 40
ctg acg ttc att gat ctg gtt atc cag gct gtc ttt ttt ggc atc tgt 196
Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys
45 50 55
gtg ctg act gat ctt tcc agt ctt ctg act cga gga agt ggg aac cag 244
Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln
60 65 70
gag caa gag agg cag ctc aag aag ctc atc tct ctc cgg gac tgg atg 292
Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile Ser Leu Arg Asp Trp Met

75 80 85

tta gct gtg ttg gcc ttt cct gtt ggg gtt ttt gtt gta gca gtg ttc 340

Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe

90 95 100 105

tgg atc att tat gcc tat gac aga gag atg ata tac ccg aag ctg ctg 388

Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu

110 115 120

gat aat ttt atc cca ggg tgg ctg aat cac gga atg cac acg acg gtt 436

Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val

125 130 135

ctg ccc ttt ata tta atc gag atg agg aca tcg cac cat cag tat ccc 484

Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro

140 145 150

agc agg agc agc gga ctt acc gcc ata tgt acc ttc tct gtt ggc tat 532

Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr

155 160 165

ata tta tgg gtg tgc tgg gtg cat cat gta act ggc atg tgg gtg tac 580

Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr

170 175 180 185

cct ttc ctg gaa cac att ggc cca gga gcc aga atc atc ttc ttt ggg 628

Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly

190 195 200

tct aca acc atc tta atg aac ttc ctg tac ctg ctg gga gaa gtt ctg 676

Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu

205 210 215

aac aac tat atc tgg gat aca cag aaa agt atg gaa gaa gag aaa gaa 724

Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu

220 225 230

aag cct aaa ttg gaa tgagatccaa gtctaaacgc aagagctaga ttgagccgcc a 780

Lys Pro Lys Leu Glu

235

ttgaagactc cttcccctcg ggcattggca gtgggggaga aaggcttca aaggaacttg 840

gtggcatcag cacccccctc ccccaatgag gacacctttt atatataaat atgtataaac 900

atagaataca gttgtttcca aaagaactca ccctcactgt gtgttaaaga attcttccca 960

aagtcattac tgataataac atttttttcc ttttctagtt ttaaaaccag aattggacct 1020

tggattttta ttttggcaat tgtaactcca tctaatcaag aaagaataaa agtttattgc 1080

acttc 1085

<210> 22

<211> 238

<212> PRT

<213> Homo sapiens

<400> 22

Met Ala Leu Val Pro Cys Gln Val Leu
1 5

Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser Ile Leu Cys Asn Tyr Lys
10 15 20 25

Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe
30 35 40

Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys
45 50 55

Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln
60 65 70

Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile Ser Leu Arg Asp Trp Met
75 80 85

Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe
90 95 100 105

Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu
110 115 120

Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val
125 130 135

Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro
140 145 150

Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr
155 160 165
Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr
170 175 180 185
Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly
190 195 200
Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu
205 210 215
Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu
220 225 230
Lys Pro Lys Leu Glu
235

<210> 23
<211> 1168
<212> DNA
<213> Homo sapiens

<400> 23
accacc atg gcc gac ccg ctg cgg gag cgc acc gag ctg ttg ctg gcc 48
Met Ala Asp Pro Leu Arg Glu Arg Thr Glu Leu Leu Leu Ala
1 5 10
gac tac ctg ggg tac tgc gcc cgg gaa ccc ggc acc ccc gag ccg gcg 96
Asp Tyr Leu Gly Tyr Cys Ala Arg Glu Pro Gly Thr Pro Glu Pro Ala
15 20 25 30
cca tcc acg ccc gag gcc gcc gtg ctg cgc tcc gcg gcc gcc agg tta 144
Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu
35 40 45
cgg cag att cac cgg tcc ttt ttc tcc gcc tac ctc ggc tac ccc ggg 192
Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly
50 55 60
aac cgc ttc gag ctg gtg gcg ctg atg gcg gat tcc gtg ctc tcc gac 240

Asn Arg Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp
65 70 75

agc ccc ggc ccc acc tgg ggc aga gtg gtg acg ctc gtg acc ttc gca 288
Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala
80 85 90

ggg acg ctg ctg gag aga ggg ccg ctg gtg acc gcc cgg tgg aag aag 336
Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys
95 100 105 110

tgg ggc ttc cag ccg cgg cta aag gag cag gag ggc gac gtc gcc cgg 384
Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg
115 120 125

gac tgc cag cgc ctg gtg gcc ttg ctg agc tcg cgg ctc atg ggg cag 432
Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln
130 135 140

cac cgc gcc tgg ctg cag gct cag ggc ggc tgg gat ggc ttt tgt cac 480
His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His
145 150 155

ttc ttc agg acc ccc ttt cca ctg gct ttt tgg aga aaa cag ctg gtc 528
Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val
160 165 170

cag gct ttt ctg tca tgc ttg tta aca aca gcc ttc att tat ctc tgg 576
Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp
175 180 185 190

aca cga tta tta tgagttttaa aacttttaac ccgcttctac ctgcccaact gt 630
Thr Arg Leu Leu

gaccaactaa atgacagatg tgtgagaaca agaactgagg gaaagcacct tccccccaccc 690
cagacgtttt tacctgaatg catacaagga gtcctgaggt ggtgatttgg ccagtgtttt 750
aacttgtgac aagtactcag gtgtgaggac aagaatgcaa atggctcttc cttgagtgaa 810
agaaatgggg agtctagagc ctctttatgc caaagaaccg cagaagaaac tgcattccat 870
taaatgggaa atacagtgct atttgctaaa acttggataa gagtgcgaac ctctcatctc 930
tccacaactt catgtgctgc tgactaattt taaacatggc cacagctggg gcaaaataat 990

ccccaaagta gaaaaagtcc cagtttaaca aagaatgtaa tgttaaaatc acttataagg 1050
aattctttga aaccaaatcc tttgaaatct aattcctggg acttctaggt ttttatagtt 1110
aacatactaa tttcttcaat aattgttaac tgcaaagttt taataaattt gtaccttt 1168

<210> 24
<211> 194
<212> PRT
<213> Homo sapiens

<400> 24

Met Ala Asp Pro Leu Arg Glu Arg Thr Glu Leu Leu Leu Ala
1 5 10
Asp Tyr Leu Gly Tyr Cys Ala Arg Glu Pro Gly Thr Pro Glu Pro Ala
15 20 25 30
Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu
35 40 45
Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly
50 55 60
Asn Arg Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp
65 70 75
Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala
80 85 90
Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys
95 100 105 110
Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg
115 120 125
Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln
130 135 140
His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His
145 150 155
Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val
160 165 170

Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp
175 180 185 190
Thr Arg Leu Leu

<210> 25
<211> 624
<212> DNA
<213> Homo sapiens

<400> 25
tttgacggaa ggagcggcgg cgacggagga ggagg atg gag gcg gtg gtg ttc 53
Met Glu Ala Val Val Phe
1 5
gtc ttc tct ctc ctc gat tgt tgc gcg ctc atc ttc ctc tcg gtc tac 101
Val Phe Ser Leu Leu Asp Cys Cys Ala Leu Ile Phe Leu Ser Val Tyr
10 15 20
ttc ata att aca ttg tct gat tta gaa tgt gat tac att aat gct aga 149
Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg
25 30 35
tca tgt tgc tca aaa tta aac aag tgg gta att cca gaa ttg att ggc 197
Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly
40 45 50
cat acc att gtc act gta tta ctg ctc atg tca ttg cac tgg ttc atc 245
His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile
55 60 65 70
ttc ctt ctc aac tta cct gtt gcc act tgg aat ata tat cga tac att 293
Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile
75 80 85
atg gtg ccg agt ggt aac atg gga gtg ttt gat cca aca gaa ata cac 341
Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His
90 95 100
aat cga ggg cag ctg aag tca cac atg aaa gaa gcc atg atc aag ctt 389

Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu
105 110 115

ggt ttc cac ttg ctc tgc ttc ttc atg tat ctt tat agt atg atc tta 437

Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu
120 125 130

gct ttg ata aat gac tgaagctgga gaagccgtgg ttgaagtcag cctacact 490

Ala Leu Ile Asn Asp
135

acagtgcaca gttgaggagc cagagacttc ttaaatcatc cttagaaccg tgaccatagc 550

agtatatatt ttcctcttgg aacaaaaaac tatttttgct gtatttttac catataaagt 610

atttaaaaaa catg 624

<210> 26

<211> 139

<212> PRT

<213> Homo sapiens

<400> 26

Met Glu Ala Val Val Phe
1 5

Val Phe Ser Leu Leu Asp Cys Cys Ala Leu Ile Phe Leu Ser Val Tyr
10 15 20

Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg
25 30 35

Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly
40 45 50

His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile
55 60 65 70

Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile
75 80 85

Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His
90 95 100

Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu
105 110 115
Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu
120 125 130
Ala Leu Ile Asn Asp
135

<210> 27
<211> 1121
<212> DNA
<213> Homo sapiens

<400> 24
gacagagggg aacaag atg gcg gcg ccg aag ggg agc ctc tgg gtg agg acc 52
Met Ala Ala Pro Lys Gly Ser Leu Trp Val Arg Thr
1 5 10
caa ctg ggg ctc ccg ccg ctg ctg ctg ctg acc atg gcc ttg gcc gga 100
Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly
15 20 25
ggt tcg ggg acc gct tcg gct gaa gca ttt gac tcg gtc ttg ggt gat 148
Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp
30 35 40
acg gcg tct tgc cac cgg gcc tgt cag ttg acc tac ccc ttg cac acc 196
Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr
45 50 55 60
tac cct aag gaa gag gag ttg tac gca tgt cag aga ggt tgc agg ctg 244
Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu
65 70 75
ttt tca att tgt cag ttt gtg gat gat gga att gac tta aat cga act 292
Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr
80 85 90
aaa ttg gaa tgt gaa tct gca tgt aca gaa gca tat tcc caa tct gat 340

Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser Gln Ser Asp
95 100 105

gag caa tat gct tgc cat ctt ggt tgc cag aat cag ctg cca ttc gct 388
Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln Leu Pro Phe Ala
110 115 120

gaa ctg aga caa gaa caa ctt atg tcc ctg atg cca aaa atg cac cta 436
Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu
125 130 135 140

ctc ttt cct cta act ctg gtg agg tca ttc tgg agt gac atg atg gac 484
Leu Phe Pro Leu Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp
145 150 155

tcc gca cag agc ttc ata acc tct tca tgg act ttt tat ctt caa gcc 532
Ser Ala Gln Ser Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala
160 165 170

gat gac gga aaa ata gtt ata ttc cag tct aag cca gaa atc cag tac 580
Asp Asp Gly Lys Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr
175 180 185

gca cca cat ttg gag cag gag cct aca aat ttg aga gaa tca tct cta 628
Ala Pro His Leu Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu
190 195 200

agc aaa atg tcc tat ctg caa atg aga aat tca caa gcg cac agg aat 676
Ser Lys Met Ser Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn
205 210 215 220

ttt ctt gaa gat gga gaa agt gat ggc ttt tta aga tgc ctc tct ctt 724
Phe Leu Glu Asp Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu
225 230 235

aac tct ggg tgg att tta act aca act ctt gtc ctc tcg gtg atg gta 772
Asn Ser Gly Trp Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val
240 245 250

ttg ctt tgg att tgt tgt gca act gtt gct aca gct gtg gag cag tat 820
Leu Leu Trp Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr
255 260 265

gtt ccc tct gag aag ctg agt atc tat ggt gac ttg gag ttt atg aat 868
Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn
270 275 280
gaa caa aag cta aac aga tat cca gct tct tct ctt gtg gtt gtt aga 916
Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg
285 290 295 300
tct aaa act gaa gat cat gaa gaa gca ggg cct cta cct aca aaa gtg 964
Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val
305 310 315
aat ctt gct cat tct gaa att taagcatttt tcttttaaaa gacaa 1010
Asn Leu Ala His Ser Glu Ile
320
gtgtaataga catctaaaat tccactcctc atagagcttt taaaatggtt tcattggata 1070
taggccttaa gaaatcacta taaaatgcaa ataaagttac tcaaatctgt g 1121

<210> 28
<211> 323
<212> PRT
<213> Homo sapiens

<400> 28
Met Ala Ala Pro Lys Gly Ser Leu Trp Val Arg Thr
1 5 10
Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly
15 20 25
Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp
30 35 40
Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr
45 50 55 60
Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu
65 70 75
Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr

80 85 90

Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser Gln Ser Asp

95 100 105

Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln Leu Pro Phe Ala

110 115 120

Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu

125 130 135 140

Leu Phe Pro Leu Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp

145 150 155

Ser Ala Gln Ser Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala

160 165 170

Asp Asp Gly Lys Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr

175 180 185

Ala Pro His Leu Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu

190 195 200

Ser Lys Met Ser Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn

205 210 215 220

Phe Leu Glu Asp Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu

225 230 235

Asn Ser Gly Trp Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val

240 245 250

Leu Leu Trp Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr

255 260 265

Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn

270 275 280

Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg

285 290 295 300

Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val

305 310 315

Asn Leu Ala His Ser Glu Ile

320

<210> 29

<211> 827

<212> DNA

<213> Homo sapiens

<400> 29

aacagcggcc ctgcggctgg cgcggcggac ggg atg agg cgc tgc agt ctc tgc 54

Met Arg Arg Cys Ser Leu Cys

1 5

gct ttc gac gcc gcc cgg ggg ccc agg cgg ctg atg cgt gtg ggc ctc 102

Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu

10 15 20

gcg ctg atc ttg gtg ggc cac gtg aac ctg ctg ctg ggg gcc gtg ctg 150

Ala Leu Ile Leu Val Gly His Val Asn Leu Leu Leu Gly Ala Val Leu

25 30 35

cat ggc acc gtc ctg cgg cac gtg gcc aat ccc cgc ggc gct gtc acg 198

His Gly Thr Val Leu Arg His Val Ala Asn Pro Arg Gly Ala Val Thr

40 45 50 55

ccg gag tac acc gta gcc aat gtc atc tct gtc ggc tcg ggg ctg ctg 246

Pro Glu Tyr Thr Val Ala Asn Val Ile Ser Val Gly Ser Gly Leu Leu

60 65 70

agc gtt tcc gtg gga ctt gtg gcc ctc ctg gcg tcc agg aac ctt ctt 294

Ser Val Ser Val Gly Leu Val Ala Leu Leu Ala Ser Arg Asn Leu Leu

75 80 85

cgc cct cca ctg cac tgg gtc ctg ctg gca cta gct ctg gtg aac ctg 342

Arg Pro Pro Leu His Trp Val Leu Leu Ala Leu Ala Leu Val Asn Leu

90 95 100

ctc ttg tcc gtt gcc tgc tcc ctg ggc ctc ctt ctt gct gtg tca ctc 390

Leu Leu Ser Val Ala Cys Ser Leu Gly Leu Leu Leu Ala Val Ser Leu

105 110 115

act gtg gcc aac ggt ggc cgc cgc ctt att gct gac tgc cac cca gga 438

Thr Val Ala Asn Gly Gly Arg Arg Leu Ile Ala Asp Cys His Pro Gly
120 125 130 135
ctg ctg gat cct ctg gta cca ctg gat gag ggg ccg gga cat act gac 486
Leu Leu Asp Pro Leu Val Pro Leu Asp Glu Gly Pro Gly His Thr Asp
140 145 150
tgc ccc ttt gac ccc aca aga atc tat gat aca gcc ttg gct ctc tgg 534
Cys Pro Phe Asp Pro Thr Arg Ile Tyr Asp Thr Ala Leu Ala Leu Trp
155 160 165
atc cct tct ttg ctc atg tct gca ggg gag gct gct cta tct ggt tac 582
Ile Pro Ser Leu Leu Met Ser Ala Gly Glu Ala Ala Leu Ser Gly Tyr
170 175 180
tgc tgt gtg gct gca ctc act cta cgt gga gtt ggg ccc tgc agg aag 630
Cys Cys Val Ala Ala Leu Thr Leu Arg Gly Val Gly Pro Cys Arg Lys
185 190 195
gac gga ctt cag ggg cag gta gta gct ggg tgt gac gca aga gtg aaa 678
Asp Gly Leu Gln Gly Gln Val Val Ala Gly Cys Asp Ala Arg Val Lys
200 205 210 215
cag aaa gcc tgg cag cca cgg ttt cct ggg att aaa gtc aaa gca tta 726
Gln Lys Ala Trp Gln Pro Arg Phe Pro Gly Ile Lys Val Lys Ala Leu
220 225 230
tgaa tatggcacta aagtgactga gctaccagac caatgatcct gtaaggcagc 780
cacagaacta aaaaacaaca attattatta aactgctctg gattctc 827

<210> 30
<211> 231
<212> PRT
<213> Homo sapiens

<400> 30

Met Arg Arg Cys Ser Leu Cys
1 5
Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu

10 15 20

Ala Leu Ile Leu Val Gly His Val Asn Leu Leu Leu Gly Ala Val Leu

25 30 35

His Gly Thr Val Leu Arg His Val Ala Asn Pro Arg Gly Ala Val Thr

40 45 50 55

Pro Glu Tyr Thr Val Ala Asn Val Ile Ser Val Gly Ser Gly Leu Leu

60 65 70

Ser Val Ser Val Gly Leu Val Ala Leu Leu Ala Ser Arg Asn Leu Leu

75 80 85

Arg Pro Pro Leu His Trp Val Leu Leu Ala Leu Ala Leu Val Asn Leu

90 95 100

Leu Leu Ser Val Ala Cys Ser Leu Gly Leu Leu Leu Ala Val Ser Leu

105 110 115

Thr Val Ala Asn Gly Gly Arg Arg Leu Ile Ala Asp Cys His Pro Gly

120 125 130 135

Leu Leu Asp Pro Leu Val Pro Leu Asp Glu Gly Pro Gly His Thr Asp

140 145 150

Cys Pro Phe Asp Pro Thr Arg Ile Tyr Asp Thr Ala Leu Ala Leu Trp

155 160 165

Ile Pro Ser Leu Leu Met Ser Ala Gly Glu Ala Ala Leu Ser Gly Tyr

170 175 180

Cys Cys Val Ala Ala Leu Thr Leu Arg Gly Val Gly Pro Cys Arg Lys

185 190 195

Asp Gly Leu Gln Gly Gln Val Val Ala Gly Cys Asp Ala Arg Val Lys

200 205 210 215

Gln Lys Ala Trp Gln Pro Arg Phe Pro Gly Ile Lys Val Lys Ala Leu

220 225 230

<210> 31

<211> 1189

<212> DNA

<213> Homo sapiens

<400> 31

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tagctgtgga accctagggt acctgttacc gcgctttggc gaaactgggt tcgctgctga   180
tttgcgaacc tttgcctgac tttctcaggc cttgagagat ctaagtaaat ttggtggccc   240
attgaaagga cctggagaga gcgtatgaag atctgcctct tctccaagaa actcaaccac   300
tagtgaca atg acc agc ctc ctg act act cct tct cca aga gaa gaa ctg    350
         Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu
         1               5                   10
atg acc acc cca att tta cag ccc act gag gcc ctg tcc cca gaa gat     398
Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp
15                  20                  25                  30
gga gcc agc aca gca ctc att gca gtt gtt atc acc gtt gtc ttc ctc     446
Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu
                35                  40                  45
acc ctg ctc tcg gtc gtg atc ttg atc ttc ttt tac ctg tac aag aac     494
Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn
            50                  55                  60
aaa ggc agc tac gtc acc tat gaa cct aca gaa ggt gag ccc agt gcc     542
Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala
        65                  70                  75
atc gtc cag atg gag agt gac ttg gcc aag ggc agc gag aaa gag gaa     590
Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu
    80                  85                  90
tat ttc atc taatgactcc caggccccaa ggagcttatt cctggctcca t           640
Tyr Phe Ile
95
cgctaacacg ttgactgctt attatgggaa agttttctct gaagccaggg agaagcattg   700
attgatgtgg gcaaatccaa gctccagcca ggtcgcagtc ccaaatgccg acatcactga   760
ctccagggac cagggacatg gagaaagctg tttatgatat ctttaaccag gccctcttac   820
tagagctggt gtttgtgact ggccaacaag atgtggctat gccaggggac atctgagtat   880
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gtgcccagtc atcttttttc acaggttgaa gggagagaaa agattttgag ttaaggtcat 940
tggctgctct actctgtccc ctacctggtc acctagtgat agccccagtg gagatactgt 1000
ccatacaagg tcttcccaga ggctggatac cacagtaaaa ggccaggcca ggaggggtag 1060
gagactatgg agatcttacc tcctgataaa tgtgctacac cccctaatct gagcccttcc 1120
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ttgctacag 1189

<210> 32
<211> 97
<212> PRT
<213> Homo sapiens

<400> 32
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1 5 10
Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp
15 20 25 30
Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu
35 40 45
Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn
50 55 60
Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala
65 70 75
Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu
80 85 90
Tyr Phe Ile
95

<210> 33
<211> 1500
<212> DNA
<213> Homo sapiens

<400> 33

ctgtgcctga gcctgagcct gagcctgagc ctgagcccga gccgggagcc ggtcgcgggg 60

gctccgggct gtgggaccgc tgggcccccca gcg atg gcg acc ctg tgg gga ggc 114

Met Ala Thr Leu Trp Gly Gly

1 5

ctt ctt cgg ctt ggc tcc ttg ctc agc ctg tcg tgc ctg gcg ctt tcc 162

Leu Leu Arg Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser

10 15 20

gtg ctg ctg ctg gcg cag ctg tca gac gcc gcc aag aat ttc gag gat 210

Val Leu Leu Leu Ala Gln Leu Ser Asp Ala Ala Lys Asn Phe Glu Asp

25 30 35

gtc aga tgt aaa tgt atc tgc cct ccc tat aaa gaa aat tct ggg cat 258

Val Arg Cys Lys Cys Ile Cys Pro Pro Tyr Lys Glu Asn Ser Gly His

40 45 50 55

att tat aat aag aac ata tct cag aaa gat tgt gat tgc ctt cat gtt 306

Ile Tyr Asn Lys Asn Ile Ser Gln Lys Asp Cys Asp Cys Leu His Val

60 65 70

gtg gag ccc atg cct gtg cgg ggg cct gat gta gaa gca tac tgt cta 354

Val Glu Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu

75 80 85

cgc tgt gaa tgc aaa tat gaa gaa aga agc tct gtc aca atc aag gtt 402

Arg Cys Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val

90 95 100

acc att ata att tat ctc tcc att ttg ggc ctt cta ctt ctg tac atg 450

Thr Ile Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met

105 110 115

gta tat ctt act ctg gtt gag ccc ata ctg aag agg cgc ctc ttt gga 498

Val Tyr Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly

120 125 130 135

cat gca cag ttg ata cag agt gat gat gat att ggg gat cac cag cct 546

His Ala Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro

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                140                 145                 150
ttt gca aat gca cac gat gtg cta gcc cgc tcc cgc agt cga gcc aac       594
Phe Ala Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn
            155                 160                 165
gtg ctg aac aag gta gaa tat gca cag cag cgc tgg aag ctt caa gtc       642
Val Leu Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val
        170                 175                 180
caa gag cag cga aag tct gtc ttt gac cgg cat gtt gtc ctc agc           687
Gln Glu Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser
    185                 190                 195
taattgggaa ttgaattcaa ggtgactaga aagaaacagg cagacaactg gaa            740
agaactgact gggttttgct gggtttcatt ttaatacctt gttgatttca ccaactgttg     800
ctggaagatt caaaactgga agcaaaaact tgcttgattt ttttttcttg ttaacgtaat     860
aatagagaca tttttaaaag cacacagctc aaagtcagcc aataagtctt ttcctatttg     920
tgacttttac taataaaaat aaatctgcct gtaaattatc ttgaagtcct ttacctggaa     980
caagcactct ctttttcacc acatagtttt aacttgactt tcaagataat tttcagggtt    1040
tttgttgttg ttgttttttg tttgtttgtt ttggtgggag aggggaggga tgcctgggaa    1100
gtggttaaca actttttca agtcacttta ctaaacaaac ttttgtaaat agaccttacc     1160
ttctattttc gagtttcatt tatattttgc agtgtagcca gcctcatcaa agagctgact    1220
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tgtgatgtct gatgcaatgc atcctagaac aaactggcca tttgctagtt tactctaaag    1400
actaaacata gtcttggtgt gtgtggtctt actcatcttc tagtaccttt aaggacaaat    1460
cctaaggact tggacacttg caataaagaa attttatttt                          1500
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<210> 34

<211> 198

<212> PRT

<213> Homo sapiens

<400> 34

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1 5
Leu Leu Arg Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser
10 15 20
Val Leu Leu Leu Ala Gln Leu Ser Asp Ala Ala Lys Asn Phe Glu Asp
25 30 35
Val Arg Cys Lys Cys Ile Cys Pro Pro Tyr Lys Glu Asn Ser Gly His
40 45 50 55
Ile Tyr Asn Lys Asn Ile Ser Gln Lys Asp Cys Asp Cys Leu His Val
60 65 70
Val Glu Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu
75 80 85
Arg Cys Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val
90 95 100
Thr Ile Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met
105 110 115
Val Tyr Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly
120 125 130 135
His Ala Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro
140 145 150
Phe Ala Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn
155 160 165
Val Leu Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val
170 175 180
Gln Glu Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser
185 190 195

<210> 35
<211> 806
<212> DNA
<213> Homo sapiens

<400> 35

gttcgtctag atttgtcggc ttgcggggag acttcaggag tcgctgtctc tgaacttcca 60

gcctcagaga ccgccgccct tgtccccgag ggcc atg ggc cgg gtc tca ggg ctt 115

Met Gly Arg Val Ser Gly Leu

1 5

gtg ccc tct cgc ttc ctg acg ctc ctg gcg cat ctg gtg gtc gtc atc 163

Val Pro Ser Arg Phe Leu Thr Leu Leu Ala His Leu Val Val Val Ile

10 15 20

acc tta ttc tgg tcc cgg gac agc aac ata cag gcc tgc ctg cct ctc 211

Thr Leu Phe Trp Ser Arg Asp Ser Asn Ile Gln Ala Cys Leu Pro Leu

25 30 35

acg ttc acc ccc gag gag tat gac aag cag gac att cag ctg gtg gcc 259

Thr Phe Thr Pro Glu Glu Tyr Asp Lys Gln Asp Ile Gln Leu Val Ala

40 45 50 55

gcg ctc tct gtc acc ctg ggc ctc ttt gca gtg gag ctg gcc ggt ttc 307

Ala Leu Ser Val Thr Leu Gly Leu Phe Ala Val Glu Leu Ala Gly Phe

60 65 70

ctc tca gga gtc tcc atg ttc aac agc acc cag agc ctc atc tcc att 355

Leu Ser Gly Val Ser Met Phe Asn Ser Thr Gln Ser Leu Ile Ser Ile

75 80 85

ggg gct cac tgt agt gca tcc gtg gcc ctg tcc ttc ttc ata ttc gag 403

Gly Ala His Cys Ser Ala Ser Val Ala Leu Ser Phe Phe Ile Phe Glu

90 95 100

cgt tgg gag tgc act acg tat tgg tac att ttt gtc ttc tgc agt gcc 451

Arg Trp Glu Cys Thr Thr Tyr Trp Tyr Ile Phe Val Phe Cys Ser Ala

105 110 115

ctt cca gct gtc act gaa atg gct tta ttc gtc acc gtc ttt ggg ctg 499

Leu Pro Ala Val Thr Glu Met Ala Leu Phe Val Thr Val Phe Gly Leu

120 125 130 135

aaa aag aaa ccc ttc tgattacctt catgacggga acctaaggac gaagcc 550

Lys Lys Lys Pro Phe

140

tacaggggca agggccgctt cgtattcctg gaagaaggaa ggcataggct tcggttttcc 610
cctcggaaac tgcttctgct ggaggatatg tgttggaata attacgtctt gagtctggga 670
ttatccgcat tgtatttagt gctttgtaat aaaatatgtt ttgtagtaac attaagactt 730
atatacagtt ttaggggaca attgagatgg ctgaactact gaataaaaaa aaaacaacgc 790
tgttttctag tcctgc 806

<210> 36
<211> 140
<212> PRT
<213> Homo sapiens

<400> 36

Met Gly Arg Val Ser Gly Leu
1 5
Val Pro Ser Arg Phe Leu Thr Leu Leu Ala His Leu Val Val Val Ile
10 15 20
Thr Leu Phe Trp Ser Arg Asp Ser Asn Ile Gln Ala Cys Leu Pro Leu
25 30 35
Thr Phe Thr Pro Glu Glu Tyr Asp Lys Gln Asp Ile Gln Leu Val Ala
40 45 50 55
Ala Leu Ser Val Thr Leu Gly Leu Phe Ala Val Glu Leu Ala Gly Phe
60 65 70
Leu Ser Gly Val Ser Met Phe Asn Ser Thr Gln Ser Leu Ile Ser Ile
75 80 85
Gly Ala His Cys Ser Ala Ser Val Ala Leu Ser Phe Phe Ile Phe Glu
90 95 100
Arg Trp Glu Cys Thr Thr Tyr Trp Tyr Ile Phe Val Phe Cys Ser Ala
105 110 115
Leu Pro Ala Val Thr Glu Met Ala Leu Phe Val Thr Val Phe Gly Leu
120 125 130 135
Lys Lys Lys Pro Phe
140

<210> 37

<211> 1718

<212> DNA

<213> Homo sapiens

<400> 37

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             Met Asn Arg Thr Asn Val Asn Val Phe Ser Glu Leu Ser
               1               5                  10
gct cct cgt cgc aat gaa gac ttt gtc ctc ctg ctc acc tac gtc ctc          98
Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu Leu Thr Tyr Val Leu
     15                  20                  25
ttc ttg atg gcg ctg acc ttc ctc atg tcc tcc ttc acc ttc tgt ggt         146
Phe Leu Met Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly
 30                  35                  40                  45
tcc ttc acg ggc tgg aag aga cat ggg gcc cac atc tac ctc acg atg         194
Ser Phe Thr Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met
                 50                  55                  60
ctc ctc tcc att gcc atc tgg gtg gcc tgg atc acc ctg ctc atg ctt         242
Leu Leu Ser Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu
             65                  70                  75
cct gac ttt gac cgc agg tgg gat gac acc atc ctc agc tcc gcc ttg         290
Pro Asp Phe Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu
         80                  85                  90
gct gcc aat ggc tgg gtg ttc ctg ttg gct tat gtt agt ccc gag ttt         338
Ala Ala Asn Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe
     95                 100                 105
tgg ctg ctc aca aag caa cga aac ccc atg gat tat cct gtt gag gat         386
Trp Leu Leu Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp
110                 115                 120                 125
gct ttc tgt aaa cct caa ctc gtg aag aag agc tat ggt gtg gag aac         434
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Ala Phe Cys Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn
                130                 135                 140
aga gcc tac tct caa gag gaa atc act caa ggt ttt gaa gag aca ggg      482
Arg Ala Tyr Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly
            145                 150                 155
gac acg ctc tat gcc ccc tat tcc aca cat ttt cag ctg cag aac cag      530
Asp Thr Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln
        160                 165                 170
cct ccc caa aag gaa ttc tcc atc cca cgg gcc cac gct tgg ccg agc      578
Pro Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser
    175                 180                 185
cct tac aaa gac tat gaa gta aag aaa gag ggc agc taactctgtc ctgaag    630
Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser
190                 195                 200
agtgggacaa atgcagccgg gcggcagatc tagcgggagc tcaaagggat gtgggcgaaa    690
tcttgagtct tctgagaaaa ctgtacaaga cactacggga acagtttgcc tccctcccag    750
cctcaaccac aattcttcca tgctggggct gatgtgggct agtaagactc cagttcttag    810
aggcgctgta gtattttttt tttttttgtc tcatccttag gatacttctt ttaagtggga    870
gtctcaggca actcaagttt agacccttac tctttttgtt tgtttttgga aacaggatct    930
tgctctgtca cccaggcttg agtgcagtgg tgcgatcaca gcccagtgca gcctcgacca    990
cctgtgctca agcaatcctc ccatctccat ctcccaaagt gctgggatga caggcgtgag   1050
ccacagctcc cagcctaggc ccttaatctt gctgttattt tccatggact aaaggtctgg   1110
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gttttgtgag gctctgtggc ccagagcaga cctgcatatc tgagcaaaaa tagcaaaagc   1230
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gccaggaatt ctttcagacc tcactagcac aagcccggtt gctccttgtc aggagaattt   1530
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tctgtaaata gatttaccgc atttacggct gcattctgta agtgggcatg gtctcctaat   1650
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cactcttt 1718

<210> 38

<211> 201

<212> PRT

<213> Homo sapiens

<400> 38

Met Asn Arg Thr Asn Val Asn Val Phe Ser Glu Leu Ser

1 5 10

Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu Leu Thr Tyr Val Leu

15 20 25

Phe Leu Met Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly

30 35 40 45

Ser Phe Thr Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met

50 55 60

Leu Leu Ser Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu

65 70 75

Pro Asp Phe Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu

80 85 90

Ala Ala Asn Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe

95 100 105

Trp Leu Leu Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp

110 115 120 125

Ala Phe Cys Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn

130 135 140

Arg Ala Tyr Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly

145 150 155

Asp Thr Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln

160 165 170

Pro Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser

175 180 185

Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser
190 195 200

<210> 39
<211> 995
<212> DNA
<213> Homo sapiens

<400> 39
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cagcgggcag cggctctcgg gctgcaggct gggcagggtc ccctcccacg ctcctgccgc 120
tgtctcccac gtcccccagg tgcgcggcca cc atg gcg tcc agc gac gag gac 173
Met Ala Ser Ser Asp Glu Asp
1 5
ggc acc aac ggc ggc gcc tcg gag gcc ggc gag gac cgg gag gct ccc 221
Gly Thr Asn Gly Gly Ala Ser Glu Ala Gly Glu Asp Arg Glu Ala Pro
10 15 20
ggc aag cgg agg cgc ctg ggg ttc ttg gcc acc gcc tgg ctc acc ttc 269
Gly Lys Arg Arg Arg Leu Gly Phe Leu Ala Thr Ala Trp Leu Thr Phe
25 30 35
tac gac atc gcc atg acc gcg ggg tgg ttg gtt cta gct att gcc atg 317
Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met
40 45 50 55
gta cgt ttt tat atg gaa aaa gga aca cac aga ggt tta tat aaa agt 365
Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser
60 65 70
att cag aag aca ctt aaa ttt ttc cag aca ttt gcc ttg ctt gag ata 413
Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile
75 80 85
gtt cac tgt tta att gga att gta cct act tct gtg att gtg act ggg 461
Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly
90 95 100

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gtc caa gtg agt tca aga atc ttt atg gtg tgg ctc att act cac agt       509
Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser
    105                 110                 115
ata aaa cca atc cag aat gaa gag agt gtg gtg ctt ttt ctg gtc gcg       557
Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala
120                 125                 130                 135
tgg act gtg aca gag atc act cgc tat tcc ttc tac aca ttc agc ctt       605
Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu
                140                 145                 150
ctt gac cac ttg cca tac ttc att aaa tgg gcc aga tat aat ttt ttt       653
Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe
            155                 160                 165
atc atc tta tat cct gtt gga gtt gct ggt gaa ctt ctt aca ata tac       701
Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr
        170                 175                 180
gct gcc ttg ccg cat gtg aag aaa aca gga atg ttt tca ata aga ctt       749
Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu
    185                 190                 195
cct aac aaa tac aat gtc tct ttt gac tac tat tat ttt ctt ctt ata       797
Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile
200                 205                 210                 215
acc atg gca tca tat ata cct ttg ttt cca caa ctc tat ttt cat atg       845
Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met
                220                 225                 230
tta cgt caa aga aga aag gtg ctt cat gga gag gtg att gta gaa aag       893
Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys
            235                 240                 245
gat gat taaatgatct ctgcaaacaa ggtgcttttt ccagaataac caagattacc t      950
Asp Asp

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25 30 35

Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met
40 45 50 55

Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser
60 65 70

Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile
75 80 85

Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly
90 95 100

Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser
105 110 115

Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala
120 125 130 135

Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu
140 145 150

Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe
155 160 165

Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr
170 175 180

Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu
185 190 195

Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile
200 205 210 215
Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met
220 225 230
Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys
235 240 245
Asp Asp